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A rare case of melorheostosis of the hand in a pediatric patient

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ABSTRACT

Melorheostosis, a rare mesenchymal dysplasia of bone, generally affects about 0.001% of people globally with about 400 cases total being reported. Melorheostosis of the hand, especially in the pediatric population, has been seldom reported. Previous studies have investigated potential genetic mutations associated with melorheostosis however, questions still remain regarding effective treatment options for this disease. This case report describes a unique case of pediatric melorheostosis of the hand and further clarifies current theories on melorheostosis with regards to pathogenesis, best treatment practices, and future research.

1. Introduction

Melorheostosis, also known as Leri's disease, is a rare mesenchymal dysplasia typically characterized by sclerotic lesions in the long bones of the upper and lower limbs. Melorheostosis of the bone, while still very uncommon, was first reported by Leri and Joanny in 1922 and described as having a “flowing candle wax” appearance.[1] According to a retrospective study done on 24 patients spanning 1972 to 2010, Leri's disease was shown to be most prevalent among middle-aged women and characterized by multiple bone involvement, with the lower extremity most commonly affected.[2] Melorheostosis of the hand, especially in the pediatric population, has been seldom reported. While the extent of involvement is variable, there is also variable function that ranges from a near normal appearance to marked loss of function. The hyperostostic bone, observed in previous reports, does not revert to normal bone, and also does not undergo malignant progression.[3] Previous cases have also described distribution of this disorder in the C6, C7 and C8 sclerotomes.[4]

Previous studies have investigated potential genetic mutations associated with melorheostosis; however, questions still remain regarding effective treatment options for this rare disease. Conservative management options include dynamic splinting and physical therapy. More invasive approaches, such as surgery, are used in the attempt to release dense fibrous contractures and improve functional impairment. However, surgical intervention has demonstrated variable results in the literature, specifically the recurrence of sclerosis and hyperostosis. Less conventional approaches have also been documented, which include the use of bisphosphonates in cases of high alkaline phosphatase.[5] The fibrotic changes observed both in the skin and soft tissues surrounding the joints present similarly to the periarticular tissues contractures characteristic of arthrogryposis multiplex congenita.[6] As a result of these tissues stretching with limb growth, they tend to recur. Thus using similar principles, contractures may be corrected through release via capsulotomy and tenotomies. Further, surgical intervention is recommended after children reach skeletal maturity, if at all possible. This paper explores a unique case of melorheostosis evaluated in a pediatric patient.

2. Case report

A right-hand dominant 7-year old male presented to the pediatric orthopaedic surgery hand clinic for evaluation of suspected melorheostosis in the right index finger. The patient was initially diagnosed with this condition two years prior when his mother noticed general deformity of the hand, specifically an enlarged index knuckle, and inability to make a full fist. He otherwise had no functional deficiencies in his hand, and hand radiographs were ordered. The previous radiographs were obtained from another medical location and demonstrated mild rotation of the index finger and slight radial deviation of the long finger (Fig. 1A and B). The recommendation was made to

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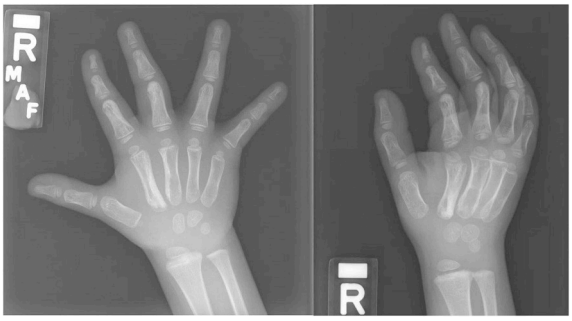

Fig. 1. A, B. Initial radiographs of a skeletally immature right hand with (A) anteriorposterior and (B) oblique views demonstrating mild rotation of the index finger and slight radial deviation of the long finger.

schedule an appointment with an orthopaedic surgeon if further changes were noted. He had complaints of difficulty making a fist a few months prior to this follow-up visit. The patient denied pain, but the patient's mother described limited range of motion of the second digit, and reported a “double-jointed” clicking of his right thumb. During the physical exam, there appeared to be mild swelling and a slight rotation of the index finger, with flexion of the metacarpophalangeal (MCP) joint to 20°.The long finger demonstrated mild radial deviation with MCP flexion to 40° and and proximal interphalangeal joint (PIP) flexion to 80°. Palpation of the soft tissues of the index and long finger appeared to be thickened on the extensor side. No motor or sensory deficits were elicited and the digits were well perfused. Radiographs were obtained at this visit, indicating slight progression of the disease (Fig. 2A, B, C). The patient's mother was reassured that this was not an emergent case, and a second opinion was suggested by the attending physician before a decision of management would be made.

The patient returned for a follow-up appointment one month later for a second opinion. On physical examination, there was slight rotation of the index finger. The index finger demonstrated 64° PIP joint flexion, 31° DIP joint flexion, with no extension deficits. The middle finger demonstrated a 93° PIP joint flexion and 64° DIP joint flexion with no extension deficits. There were no motor or sensory deficits, and the digits were will perfused. Evaluation of AP and lateral radiographs of the right hand displayed evidence of melorheostosis on the ulnar border of the index metacarpal and the radial border of the long metacarpal. The right index finger DIP deviated to 160° from a 2011 evaluation of 159°, while the middle finger middle phalanx progressed to 170° from 164° in the 2011 evaluation. As a result of the minimal progression noted, surgical intervention was not recommended, as the risks outweighed the benefits. A plan was made to follow-up in 2 years with repeated radiographs.

3. Discussion

Melorheostosis of the hand, particularly in the pediatric population, is very rare. Children and adults often present with different clinical features. Children often have asymmetric limb contractures while adults commonly complain of pain as the most presenting concern.[3] Similarly, review of literature reveals adults often present with progressive deformities.[7] Our patient's mesenchymal dysplasia was non-painful with minimal progression. Furthermore, standardized treatment for melorheostosis has not been fully elucidated. One study of melorheostosis in the thumb and trapezium of an adult female with painful symptoms employed surgical debulking of the hyperostotic cortex and cortical fenestration.[8] In our patient, we recommended conservative treatment with close follow-up and refrained from recommending acute surgical intervention in the absence of pain and functional impairment. Consequently, a clear understanding of the pathogenesis is key to influencing treatment decisions.

One of the main questions regarding melorheostosis is the pathogenesis. There are many theories that have attempted to characterize the development of this disease - mainly embryological manifestation, mosaicism (in relation to Osteopoikilosis and Buschke-Ollendorff syndrome), and genetic mutation. There is suspicion that during embryonic development, an abnormal sensory spinal nerve (derived from neural crest) may be compromised or damaged affecting a particular sclerotome, eventually presenting as a bony overgrowth in the corresponding region.[9] This theory was proposed in a reported case of shoulder melorheostosis in a patient with a left scapular lesion within the boundaries of the C6 sclerotome.[9] It has also been suggested that there is an element of mosaicism involved, uncovering a family with three generations of osteopoikilosis (5 individuals) and one generation (one individual) of melorheostosis.[10] Osteopoikilosis is cited as an autosomal dominant condition associated with a loss of function mutation in LEMD3 gene along with related disease, Buschke-Ollendorff syndrome. Though it has been theorized that osteopoikilosis and Buschke-Ollendorff syndrome are related to melorheostosis via LEMD3, a recent article by Kang et al. suggests that the LEMD3 gene may not be the prime genetic agent since the loss of function mutation has not been seen in the more prevalent sporadic melorheostosis.[11] In their study of the bone of 15 biopsied patients with melorheostosis, eight patients expressed mutations in the MAPK21 oncogene, more specifically missense, activating mutations in the negative regulatory region of MAP2K1, referred to as MEK1. Inhibition of MEK1 may demonstrate capacity as a target for melorheostosis therapy.[11]

Secondary to the undefined clinical pathogenesis of melorheostosis,

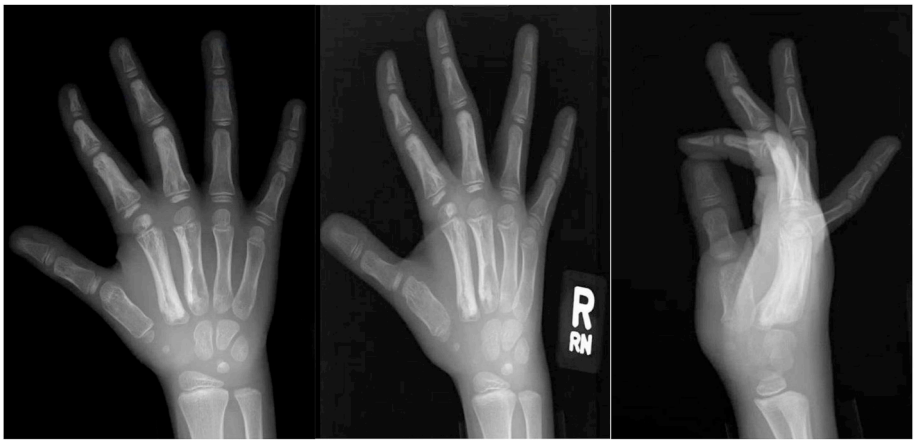

Fig. 2. A, B, C. Radiographs of a skeletally immature right hand with (A) anteroposterior, (B) oblique, and (C) lateral views demonstrating melorheostosis of cortical borders of the 2nd and 3rd metacarpals, as well as involvement of the proximal, middle, and distal phalanges of the 2nd and 3rd digits.

there exists an ongoing effort to establish definitive treatment guidelines for the morbidity associated with this ailment. Melorheostosis is characterized by a wide range of clinical pathology including gross deformity of the involved extremity, limb stiffness, joint restriction due to contracture, and limb shortening. The debilitating effects of this disease are oftentimes treated surgically using methods including tendon lengthening, excision of fibrous and osseous tissues, and joint contracture release.[12] While these surgical methods are well-employed, recurrence rates and continued pain experienced by patients have forced physicians to look for alternate forms of treatment. Non-surgical methods including physical therapy (stretching exercises and analgesics) and neuropathic pain medications (to treat pain from neural compression) have been employed with varying levels of success at pain control.[13] Most recently, studies have pointed to bisphosphonates as a viable therapeutic option in terms of pain control, suppression of disease markers, and prevention of bone turnover owing to the drug class's anti-osteoclastic effects.[14] The evidence for the use of bisphosphonates in children with melorheostosis, however, remains unclear.

In the current literature, it is not shown that melorheostosis is associated with increased patient mortality, but rather contributes heavily to functional morbidity.[15] Given the multitude of ways in which melorheostosis presents clinically, patient outcomes are often correlated with the severity of the disease, its anatomic location, surrounding structural involvement, and its impact on individual patients' quality of life. While this variability precludes a definitive prognosis, the disease is typically measured based on factors determining the extent to which the disease has progressed including the age of the patient and the likelihood of recurrence. It is well documented that melorheostosis progresses more rapidly in children, slows in adulthood, and thus will affect younger patients more significantly over the course of their lives.[15,16] Melorheostosis is also well-known for its recurrence rate. A study performed by the Mayo Clinic revealed that even primary surgical intervention can prove inadequate, with such patients requiring additional intervention at rates as high as 54%.[17] Thus, the important discussion regarding definitive treatment continues, with novel clinical reports and research further defining the etiology, progression, and management of this disease.

3.1. Future of research

There are many questions driving future melorheostosis research, mostly focused on disease etiology and treatment. The progression of melorheostosis requires better characterization on the genetic and clinical level – whether it be mutation, mosaicism, sclerotomes, or some combination, ideally via longitudinal study. A clinical staging system could potentially be developed. One study confirmed that after 24 years follow-up, a case of melorheostosis in the left arm was strictly limited to a dermatome supplied by the associated spinal nerve. More longitudinal studies are needed to confirm etiology. A major barrier pinpointing the cause of melorheostosis is its varying symptomatology and rarity. The "dripping candle wax" appearance is not all inclusive, as reported in only five of 24 cases in Mayo Clinic's retrospective study where surgical treatment often led to additional surgery.

Research should also address the outcomes of surgery versus isolated pharmacological treatment. Many pharmacological options have been approached – from the more popular bisphosphonates to denosumab and even nifedipine. Nifedipine lends credence to exploring the vascularity of melorheostosis. In a 1963 study by Morris et al., biopsy of melorheostosis done at diagnosis and 18 years later showed possible progression from vasculitis to vascular obliteration.[18] The vascular component of melorheostosis has limited evidence and may play a large role in the symptomatology of MAP2K1+ melorheostosis. Eight MAP2K1+ patients were compared to seven MAP2K1- patients via biopsy of bone. Notably, they found that the MAP2K1+ patients were more likely to have the classic candle wax appearance on radiographs along with a vasculo-cutaneous lesion near the site of melorheostosis. This gene, as noted earlier in our discussion, again presents as quite possibly the key focus of future research due to its implications in both etiology and treatment.

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